

### **REMARKS**

Reconsideration of this application is respectfully requested in light of the above amendments and accompanying remarks.

#### **Status of the Claims**

Upon entry of this amendment, claims 2-23, 36, 39-41, 43, 45-51, 53-57, 59, 66 and 71, 73, 75 and 77, 80-82, 84 and 86-90 will be pending and at issue in this application. Claims 72, 74 and 76, 78, 79, 83 and 85 have been canceled without prejudice or disclaimer. Claim 59 has been amended recite that the first composition comprises a mixture of PEG and poloxamer. Support for this amendment can be found in the paragraph spanning pp. 13-14 of the application, as filed. No new matter has been added by this amendment.

#### **Indefiniteness Rejection**

Claims 2-23, 36, 39-41, 43, 45-51, 53-57, 59, 66 and 71-75 are rejected as indefinite. The Examiner argues that it is unclear what actions are carried out in optional step (ii) of claim 59, which recites “bringing the first composition in liquid form.” In the Examiner’s view, it is unclear if something is being brought from one location to another or if the materials are brought into a particular state, such as a liquid state. In response, optional step (ii) of claim 59 has been amended to call for “bringing the first composition into liquid form.” Support for this amendment can be found, for example, at p. 12, ll. 10-37 of the application, as filed. In view of this amendment, it is clear that optional step (ii) of claim 59 calls for the materials to be brought into a particular state, rather than transporting the materials from one location to another. Accordingly, Applicants request withdrawal of this rejection.

Claim 74 is rejected as indefinite. Claim 74 has been canceled. Therefore, this rejection has been rendered moot.

**Obviousness Rejection**

Claims 2-23, 36, 39-41, 43, 45-51, 53-57, 59, 66 and 71-90 are rejected as obvious over WO 03/004001 (“WO ‘001”) in view of U.S. Patent No. 6,576,259 (“the ‘259 Patent”) and the Merck Index entry for tacrolimus (which discloses tacrolimus’ melting point). The Examiner contends that it would have been obvious to use tacrolimus and HPMC in the process described in WO ‘001 in view of the ‘259 Patent.

The present claims call for dispersing tacrolimus in a first composition comprising PEG and poloxamer, spraying the first composition onto a second composition, and adding a release-rate modifier by dry mixing (*see* claim 59). WO ‘001 does not disclose dispersing tacrolimus in a mixture of PEG and poloxamer or adding a release-rate modifier after the dispersion has been sprayed onto a second composition. The Examiner cites the ‘259 Patent to cure the deficiencies of WO ‘001. However, the ‘259 Patent teaches away from dispersing tacrolimus in a mixture of PEG and poloxamer. For example, the ‘259 Patent teaches that in order to arrive at a sustained release tacrolimus composition, the following steps are employed:

the macrolide compound is dissolved in an organic solvent, followed by addition of an appropriate amount of a solid base [such as HPMC], and the resulting mixture is sufficiently dissolved or suspended together or is allowed to swell.

(the ‘259 Patent, col. 11, ll. 4-9).

Based on these teachings, one of ordinary skill in the art would not have used a mixture of PEG and poloxamer as a vehicle for tacrolimus, in a sustained release tacrolimus composition. Rather, the ordinary skilled artisan would have used an organic solvent and a solid base (such as HPMC), as taught by the ‘259 Patent. The Examiner has not provided any teaching or suggestion that the organic solvent method taught by the ‘259 Patent is compatible with the use of a PEG/poloxamer mixture. Further, the Examiner has failed to provide any teaching or suggestion as to how to combine the components in the presently claimed arrangement to arrive at a functional sustained release tacrolimus composition. Therefore, the Examiner has failed to meet her burden in establishing a *prima facie* case of obviousness against the pending claims. “[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be

some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR v. Teleflex*, 550 U.S. 398, 418 (2007), citing, *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006).

Additionally, neither WO ‘001 nor the ‘259 Patent disclose or suggest adding at least one release-rate modifier to a composition of tacrolimus in a mixture of PEG and poloxamer by dry mixing. WO ‘001 is silent with regard to the addition of a release-rate modifier. The ‘259 Patent does not cure this deficiency. Rather, the ‘259 Patent teaches the use of an aqueous solution of HPMC. *See* the ‘259 Patent at col. 9, ll. 1-15 and examples 1, 2 and 4. As stated above, the ‘259 Patent teaches:

the macrolide compound is dissolved in an organic solvent, followed by addition of an appropriate amount of a solid base [HPMC], and the resulting mixture is sufficiently dissolved or suspended together or is allowed to swell.

(the ‘259 Patent, col. 11, ll. 4-9).

Therefore, the ‘259 Patent does not teach or suggest dry mixing HPMC with the resulting composition. One of ordinary skill in the art, upon considering this teaching in combination with WO ‘001, would not have dry mixed a release-rate modifier with tacrolimus in a PEG/poloxamer mixture. The Examiner has not provided any rationale as to why one of ordinary skill in the art would have modified the teachings of the ‘259 Patent to arrive at the presently claimed invention. Nor has the Examiner provided any rationale as to why the ordinary skilled artisan would have selectively picked particular substances from WO ‘001 as a vehicle for tacrolimus, instead of the ethanol and HPMC as taught in the ‘259 Patent.

Accordingly, it appears that the Examiner is using impermissible hindsight to reconstruct the present invention by picking and choosing elements from the different references when there is no motivation to combine any one or more of their respective disclosures into a single embodiment. In *KSR v. Teleflex*, the Supreme Court held that “a factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.” *KSR v. Teleflex*, 550 U.S. 398, 421 (2007). The Examiner’s reasoning appears to fall into the area that the *KSR* court explicitly warned against.

Applicants also note that claims 83-85 and 90 are product-by-process claims. Because the compositions taught by the combination of WO '001 and the '259 Patent are made by a different process from that disclosed in the present application, and contain different components, the compositions of the prior art combination are necessarily, structurally different from the presently claimed compositions. As stated above, there is no teaching or suggestion in the cited references that would lead the ordinary skilled artisan to the presently claimed methods. Therefore, the product-by-process claims are not obvious over the combination of WO '001 and the '259 Patent.

For the foregoing reasons, Applicants respectfully request withdrawal of this rejection.

**CONCLUSION**

Based on the above amendments and arguments, this application is believed to be in condition for allowance, which is earnestly solicited. If there are remaining issues that the Examiner believes could be addressed by conducting an interview or entering an Examiner's Amendment, the Examiner is cordially invited to contact the undersigned agent to discuss such issues.

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